REMARKS

The Claims

Claims 1-60 originally presented in this continuation application were subject to a restriction requirement (Paper No. 5). Applicants in their response of April 23, 2002 (Paper No. 6) elected the invention corresponding to Group IV, Claims 39-41 with the non-elected claims being withdrawn from consideration by the Examiner.

Applicants hereby cancel Claims 1-60 without prejudice and disclaimer and add new Claims 61-75. The new claims are directed in part to antibodies or fragments thereof which bind to an epitope comprising at least a portion of an amino acid sequence of SEQ ID NO:121, SEQ ID NO:123, or SEQ ID NO:125; and to methods of detecting OPG and removing OPG in biological samples using said antibodies. The new claims are fully supported by the specification and do not introduce new matter.

Specifically, support for an antibody which binds "an epitope comprising at least a portion of the amino acid sequence of ... " is found at p. 31, lines 11-14 (discloses that antibodies may be generated using peptides which span a portion of the OPG sequence, and consequently bind to said portion) and p. 31, lines 21-23 (discloses characterization of the epitope recognized by the antibodies). Support for Claim 75 is found at p. 31, line 33 to p. 32, line 2.

Entry of the new claims is respectfully requested.

Title of the Invention

The Examiner has required a new title which is clearly indicative of the invention to which the claims are directed. Applicants will amend the title in due course upon an indication of allowable subject matter by the Examiner.

Disclosure of Nucleotide and/or Amino Acid Sequences

The Examiner has indicated that the application fails to comply with the requirements for disclosure of nucleotide and/or amino acid sequences as set forth in 37 CFR 1.821-1.825. Applicants have amended the application to introduce sequence identifiers for the various figures noted by the Examiner. In addition, Applicants are submitting herewith a substitute paper copy of the sequence listing and computer readable form thereof in order to correct the discrepancy in SEQ ID NO:135 noted by the

Examiner. It is believed that the application is now in compliance with the requirements of 37 CFR 1.821-1.825.

Objection to the specification

The disclosure has been objected to as there is no reference to Figure 16A and Figure 16B in the description of the figures on p. 10. The application has been amended to include such references.

Rejections under 35 U.S.C. 112

Claims 39-41 are rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly does not enable one to make and/or use the invention commensurate with the scope of the claims. The Examiner argues that the claims are overly broad because the specification fails to teach "all species of OPG protein in order to generate antibodies against these species" and "any variant of OPG in order to generate antibodies". The Examiner contends it would require undue experimentation to make all such OPG polypeptides to generate the claimed antibodies. Applicants disagree.

The Examiner argues that in order to enable the claimed antibodies, the specification must enable the making and using of all OPG polypeptides that could be immunogens. This is simply incorrect. In the first instance, the claims are directed to an antibody which binds to an OPG polypeptide, not to the OPG polypeptide itself. Accordingly, it is the making and using of the antibodies that must be enabled. Secondly, the Examiner's argument ignores what was known in the art regarding the binding properties of antibodies. The skilled worker recognized at the time of filing of the application that antibodies bind particular epitopes on a polypeptide. It was also recognized that antibodies were capable of binding to different polypeptides which are nonetheless related by harboring the epitope recognized by the antibody. Thus, using the structure of OPG as provided in the present application, one skilled in the art can generate an antibody using a particular OPG polypeptide as an immunogen with the knowledge that such an antibody can bind to related OPG polypeptides which retain the binding epitope. Such polypeptides are readily identified by, for example, making OPG variants and testing such variants for their ability to bind to an antibody generated by a particular immunogen. Such an approach (and other similar approaches) is well within the level of skill in the art is not undue experimentation. In view of the guidance in the specification relating to the structure of OPG, the state of the art with respect to the binding properties of antibodies, and the level of skill exhibited in the

field of antibody production, it is clear that undue experimentation is not required to practice the claimed invention over its entire scope.

Applicants also note that the specification provides an extensive disclosure not only of OPG polypeptides of SEQ ID NO:121, SEQ ID NO:123 and SEQ ID NO:125, but also numerous fragments, variants, derivatives and analogs (see Example 7 starting on p. 59; Example 8 starting on p. 76; and Example 9 starting on p. 111 of the specification). Moreover, a three dimensional structure model of OPG as set forth in Example 6 allows for the identification of amino acid residues in the four cysteine rich domains of OPG that are involved in activity and are important for structure. In view of this extensive disclosure, the Examiner's position that the application is enabling for only OPG of SEQ ID NO:121, SEQ ID NO:123 and SEQ ID NO:125 is without any support whatsoever.

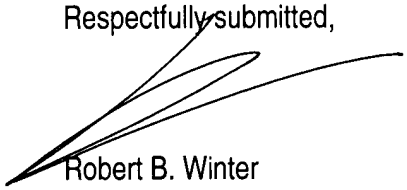
Withdrawal of the rejection is requested.

Claims 39-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for recitation of the term "OPG". This rejection is moot in view of the cancellation of Claims 39-41.

CONCLUSION

Claims 61-75 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,



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VERSION SHOWING CHANGES

At page 4:

Figure 1. A. FASTA analysis of novel EST LORF. Shown is the deduced FRI-1 amino acid sequence aligned to the human TNFR-2 sequence (SEQ ID NO: 169 and 170). B. Profile analysis of the novel EST LORF shown is the deduced FRI-1 amino acid sequence aligned to the TNFR-profile (SEQ ID NO: 171 and 173). C. Structural view of TNFR superfamily indicating region which is homologous to the novel FRI-1.

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Figure 2. Structure and sequence of full length rat OPG gene, a novel member of the TNFR superfamily. A. Map of pMOB-B1.1 insert. Box indicates position of LORF within the cDNA sequence (bold line). Black box indicates signal peptide, and gray ellipses indicate position of cysteine-rich repeat sequences. B, C. Nucleic acid and protein sequence of the Rat OPG cDNA. The predicted signal peptide is underlined, and potential sites of N-linked glycosylation are indicated in bold, underlined letters (SEQ ID NO: 120 and 121). D, E. Pileup sequence comparison (Wisconsin GCG Package, Version 8.1) of OPG with other members of the TNFR superfamily, fas (SEQ ID NO:128); tnfr1 (SEQ ID NO: 129); sfu-t2 (SEQ ID NO:130); tnfr2 (SEQ ID NO:131); cd40 (SEQ ID NO:132); osteo (SEQ ID NO:133); ngfr (SEQ ID NO:134); ox40 (SEQ ID NO:135); 41bb (SEQ ID NO:136).

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Figure 9. Structure and sequence of mouse and human OPG cDNA clones. A, B. Mouse cDNA and protein sequence (SEQ ID NOs. 122 and 123). C, D. Human cDNA and protein sequence (SEQ ID NOs: 124 and 125). The predicted signal peptides are underlined, and potential sites of N-linked glycosylation are indicated in bold. E, F. Sequence alignment and comparison of rat (SEQ ID NO: 174), mouse (SEQ ID NO: 175) and human (SEQ ID NO: 176) OPG amino acid sequences.

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Figure 10. Comparison of conserved sequences in extracellular domain of TNFR-1 and human OPG. PrettyPlot (Wisconsin GCG Package, Version 8.1) of the TNFR1 and OPG alignment described in example 6. Top line, human TNFR1 sequences encoding domains 1-4 (SEQ ID NO: 177). Bottom line, human OPG sequences encoding domains 1-4 (SEQ ID NO: 178). Conserved residues are highlighted by rectangular boxes.

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Figure 12. Structure of OPG cysteine-rich domains. Alignment of the human (top line SEQ ID NO:136) and mouse (bottom line SEQ ID NO: 179) OPG amino acid sequences

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Figure 16. Pulse-chase analysis of recombinant murine OPG produced in CHO cells. CHO cells were pulse-labeled with ^{35}S-methionine/cysteine, then chased for the indicated time. Metabolically labeled cultures were separated into both conditioned media and cells, and detergent extracts were prepared from each, clarified, then immunoprecipitated with anti-OPG antibodies. The immunoprecipitates were the resolved by SDS-PAGE, and exposed to film. A. Top left and right panels; samples analyzed under non-reducing conditions. B. Lower left and right panels; samples analyzed under reducing conditions. Top and bottom left panels; Cell extracts. Top and bottom right panels; Conditioned media extracts. The relative mobility of the 55 kd monomeric and 100 kd dimeric forms of OPG are indicated by arrowheads.